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References

Advisory Group on Ionising Radiation. 2010. Circulatory Disease Risk. Report of the Independent Advisory Group on Ionising Radiation. London:Health Protection Agency. Available: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1284475204588 [accessed 8 November 2012].

Burnham KP, Anderson DR. 1998. Model Selection and Multimodel Inference: A Practical Information-Theoretic Approach. 2nd ed. New York:Springer.

Little MP, Azizova TV, Bazyka D, Bouffler SD, Cardis E, Chekin S, et al. 2012. Systematic review and meta-analysis of circulatory disease from exposure to low-level ionizing radiation and estimates of potential population mortality risks. Environ Health Perspect 120:1503–1511.

Little MP, Tawn EJ, Tzoulaki I, Wakeford R, Hildebrandt G, Paris F, et al. 2010. Review and meta-analysis of epidemiological associations between low/moderate doses of ionizing radiation and circulatory disease risks, and their possible mechanisms. Radiat Environ Biophys 49:139–153.

Mitchel RE, Hasu M, Bugden M, Wyatt H, Little MP, Gola A, et al. 2011. Low-dose radiation exposure and atherosclerosis in *ApoE*$^{-/-}$ mice. Radiat Res 175:665–676.

Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. 2003. Studies of mortality of atomic bomb survivors. Report 13: solid cancer and noncancer disease mortality: 1950–1997. Radiat Res 160:381–407.

Rödel F, Frey B, Gaipl U, Keilholz L, Fournier C, Manda K, et al. 2012. Modulation of inflammatory immune reactions by low-dose ionizing radiation: molecular mechanisms and clinical application. Curr Med Chem 19:1741–1750.

Schöllnberger H, Kaiser JC, Jacob P, Walsh L. 2012. Dose-responses from multi-model inference for the non-cancer disease mortality of atomic bomb survivors. Radiat Environ Biophys 51:165–178.

Shimizu Y, Kodama K, Nishi N, Kasagi F, Suyama A, Soda M, et al. 2010. Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950–2003. BMJ 340:b5349; doi: http://dx.doi.org/10.1136/bmj.b5349 [Online 14 January 2010].

Is Ambient $PM_{2.5}$ Sulfate Harmful?

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Lepeule et al. (2012) associated reduced $PM_{2.5}$ (particulate matter ≤ 2.5 μm in aerodynamic diameter) with decreased mortality over almost four decades. Because the sulfate/$PM_{2.5}$ ratio dropped among six localities but the $PM_{2.5}$ mortality coefficient did not "substantially" increase, the authors concluded that sulfate must be "about as toxic" as average $PM_{2.5}$. In a two-pollutant world, perhaps.

When a single source emits several $PM_{2.5}$ species, and a specific species is emitted from several sources, chemical-specific associations might not reflect inherent toxicity but rather status as a marker of harmful coemissions (Grahame and Hidy 2007; Mostofsky et al. 2012). Furthermore, because total $PM_{2.5}$ is often associated with adverse health outcomes, association of a constituent representing a large portion of total mass (e.g., sulfate) may occur unrelated to any inherent toxicity (Mostofsky et al. 2012).

Toxicological studies have not indicated adverse health effects from sulfate per se (Schlesinger and Cassee 2003). However, reducing a unit of black carbon (BC) increased life expectancy 4–9 times more than reducing a unit of $PM_{2.5}$ (Janssen et al. 2011). Evidence from both toxicological and human panel studies with accurate subject exposure consistently has linked BC with adverse cardiovascular health outcomes (Grahame and Schlesinger 2010). Metals and other emissions from older steel plants are particularly toxic (Dye et al. 2001).

Substantial reductions in BC and polycyclic aromatic hydrocarbons from diesel engines and coke ovens, various metals from steel plants, and nickel and vanadium from residual oil have occurred over the time frame examined by Lepeule et al. (2012). Sulfur was coemitted by all of these sources. Because less abundant but more toxic $PM_{2.5}$ species were also substantially reduced over this period, changes in the sulfate/$PM_{2.5}$ ratio as applied to mortality might reflect toxicity of coemissions, not of sulfate. Is sulfate inherently toxic or merely a coemission of harmful PM species?

Researchers must use models that include many relevant $PM_{2.5}$ species to successfully parse adverse health effects of each (Grahame and Hidy 2007). BC (and to a lesser extent nickel) remains consistently associated with adverse health outcomes when increasingly sophisticated models—all including 18 $PM_{2.5}$ species—are used; however, sulfate associations become negative and insignificant (Mostofsky et al. 2012).

Further, subject exposure measures must be reasonably accurate; associations found with accurate exposure may not be found when central monitor concentrations are proxies for exposure across a metropolitan area (Suh and Zanobetti 2010).

Human panel studies can examine effects of $PM_{2.5}$ species with more accurate subject exposure. Schwartz et al. (2005) found consistent associations for measures of heart rate variability with BC, but fewer associations for $PM_{2.5}$. In that study, the authors used an algorithm separating BC from $PM_{2.5}$ and found no associations with the $PM_{2.5}$ remainder (termed "secondary $PM_{2.5}$" by the authors), which would include both secondary sulfate and its reaction products.

Any conclusions regarding sulfate toxicity are premature until consistent results from advanced models (Mostofsky et al. 2012), which are able to examine many chemical species and incorporate good exposure measures, are available and are congruent with toxicology.

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References

Dye JA, Lehmann JR, McGee JK, Winsett DW, Ledbetter AD, Everitt JI, et al. 2001. Acute pulmonary toxicity of particulate matter filter extracts in rats: coherence with epidemiological studies in Utah Valley residents. Environ Health Perspect 109(suppl 3):395–403.

Grahame T, Hidy GM. 2007. Pinnacles and pitfalls for source apportionment of potential health effects from airborne particle exposure. Inhal Toxicol 19:727–744.

Grahame TJ, Schlesinger RB. 2010. Cardiovascular health and particulate vehicular emissions: a critical evaluation of the evidence. Air Qual Atmos Health 3:3–27.

Janssen, NAH, Hoek G, Simic-Lawson M, Fischer P, van Bree L, ten Brink H, et al. 2011. Black carbon as an additional indicator of the adverse health effects of airborne particles compared with PM_{10} and $PM_{2.5}$. Environ Health Perspect 119:1691–1699.

Lepeule J, Laden F, Dockery D, Schwartz J. 2012. Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities Study from 1974 to 2009. Environ Health Perspect 120:965–970.

Mostofsky E, Schwartz J, Coull BA, Koutrakis P, Wellenius GA, Suh HH, et al. 2012. Modeling the association between particle constituents of air pollution and health outcomes. Am J Epidemiol 176(4):317–326.

Schlesinger RB, Cassee F. 2003. Atmospheric secondary inorganic particulate matter: the toxicological perspective as a basis for health effects risk assessment. Inhal Toxicol 15:197–235.

Schwartz J, Litonjua A, Suh H, Verrier M, Zanobetti A, Syring M, et al. 2005. Traffic related pollution and heart rate variability in a panel of elderly subjects. Thorax 60:455–461.

Suh HH, Zanobetti A. 2010. Exposure error masks the relationship between traffic-related air pollution and heart rate variability. J Occup Env Med 52 (7):685–692.

Is Ambient $PM_{2.5}$ Sulfate Harmful? Schwartz and Lepeule Respond

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Grahame and Schlesinger make two arguments against the conclusions of our paper (Lepeule et al. 2012). Regarding their first point, we argued that if sulfates are nontoxic—and the fraction of particles that are

sulfate has declined substantially since the 1970s—one would expect a slope to have increased over time because the nontoxic fraction of PM (particulate matter) mass was declining. Grahame and Schlesinger make no concrete argument against it, other than to say that it conflicts with the approaches we advocated in another paper (Mostofsky et al. 2012). This is not true.

To see this, let us put our argument more mathematically. Consider the model

$$\log(\text{hazard ratio}) = b_0 + b_1(t)\text{PM}_{2.5}, \quad [1]$$

where b_0 is the baseline hazard and $b_1(t)$ is the possibly time varying slope of $PM_{2.5}$. We said that if sulfates (SO_4) had no toxicity and the ratio changed over time, we would expect

$$b_1(t) = c_1 + c_2(\text{SO}_4/\text{PM}_{2.5})_t, \quad [2]$$

and because $b_1(t)$ has no time trend, c_2 is zero. By substitution we obtain

$$\log(\text{hazard ratio}) = b_0 + c_1\text{PM}_{2.5} + c_2\text{SO}_4, \quad [3]$$

which is precisely the model that we advocated in Mostofsky et al. (2012). If c_2 is zero, then sulfates are neither more nor less toxic than average, which is the conclusion we drew in our paper (Lepeule et al. 2012).

Regarding the second point, we believe that the toxicity of ammonium sulfate per se misses the more general point: What does the addition of acidic sulfates into the atmosphere do to produce particles that are toxic? A typical process involves the sulfur dioxide (SO_2) emissions from a coal-burning power plant being converted into sulfuric acid. This acid—or products formed from it—coats the outside of other particles (or adsorbs them), such as metal oxide particles from, for example, brake wear of cars and trucks, from tire wear, or from metal processing. Through internal mixing, the surface components diffuse into the inside of the particles; the acidic sulfates react with the metals, converting insoluble (and hence low toxicity) metal oxides into metal ions that are readily soluble in the lung lining fluid. This is critical because transition metals can catalytically induce the production of highly reactive oxygenating compounds.

Ghio et al. (1999) reported that soluble iron concentrations correlate with sulfate concentrations in particles, and that the ability of soluble extracts from the particles to generate damaging oxidants was directly proportional to the sulfate concentrations. Rubasinghege et al. (2010) simulated the transformation of nonbioavailable iron to dissolved iron in atmospheric iron particles in the presence of acids, and found that the presence of sulfuric acid on the particles resulted in a dramatic increase in the bioavailable iron.

Transformations of metal particles are not the only way sulfates transform particles. Elemental carbon particles undergo chemical modification over time. Popovicheva et al. (2011) showed that the extent of water uptake and modification of elemental carbon particles depended on the sulfate content of the particles. In addition, Li et al. (2011) reported that sulfate aided the aging of freshly emitted soot particles.

It is clear that sulfates contribute to the formation of secondary organic particles. For example, Wu et al. (2007) examined the effect of ammonium sulfate aerosol on the photochemical reactions of toluene (mostly from cars) and nitrogen oxides to form those secondary organic particles. They found that the sulfate particles reduced the time to reach maximum concentrations of secondary organic aerosols and also increased the total aerosol yield from toluene. That is, in the presence of sulfates, more gaseous emissions from mobile sources were converted into particles.

Hence there is good reason to believe that SO_2 emissions and consequent sulfate particles in the air cause an increase in the number and toxicity of particles in the air that is proportional to the amount of sulfate, which makes the many epidemiologic findings of toxicity associated with sulfate quite plausible.

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References

Ghio AJ, Stoneheurner J, McGee JK, Kinsey JS. 1999. Sulfate content correlates with iron concentrations in ambient air pollution particles. Inhal Toxicol 11:293–307.

Lepeule J, Laden F, Dockery D, Schwartz J. 2012. Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities Study from 1974 to 2009. Environ Health Perspect 120:965–970.

Li W, Shao L, Shen R, Yang S, Wang Z, Tang U. 2011. Internally mixed sea salt, soot, and sulfates at Macao, a coastal city in South China. J Air Waste Manag Assoc 61:1166–1173.

Mostofsky E, Schwartz J, Coull BA, Koutrakis P, Wellenius GA, Suh HH, et al. 2012. Modeling the association between particle constituents of air pollution and health outcomes. Am J Epidemiol 176:317–326.

Popovicheva OB, Persiantseva NM, Kireeva ED, Khokhlova TD, Shonija NK. 2011. Quantification of the hygroscopic effect of soot aging in the atmosphere: laboratory simulations. J Phys Chem A 115:298–306.

Rubasinghege G, Lentz RW, Scherer MM, Grassian VH. 2010. Simulated atmospheric processing of iron oxyhydroxide minerals at low pH: roles of particle size and acid anion in iron dissolution. Proc Natl Acad Sci USA 107:6628–6633.

Wu S, Hao JM, Lu ZF, Zhao Z, Li JH. 2007. Effect of ammonium sulfate aerosol on the photochemical reaction of toluene/NO(x)/air mixture [in Chinese]. Huan Jing Ke Xue 28:1183–1187.

Errata

Joubert et al. [Environ Health Perspect 120:1425–1431 (2012)] have reported errors in their paper, "450K Epigenome-Wide Scan Identifies Differential DNA Methylation in Newborns Related to Maternal Smoking During Pregnancy." In Figure 2, the gene name for the last CpG listed, cg12477880, should have been *RUNX1* instead of *CYP1A1*. In Table 3, the percent differences in median methylation (smokers – nonsmokers) were incorrect for two CpGs; the correct values are –1.2 (MoBa) and –1.1 (NEST) for *TTC7B* cg18655025, and –1.8 (MoBa) and –0.3 (NEST) for *HLA-DPB2* cg11715943. These values are presented correctly in Figure 2. *EHP* and the authors regret the errors.

Li et al. have provided an update for their paper "Differential Estrogenic Actions of Endocrine-Disrupting Chemicals Bisphenol A, Bisphenol AF, and Zearalenone through Estrogen Receptor α and β *in Vitro*" [Environ Health Perspect 120:1029–1035 (2012)]. Recent analysis indicates that the mouse ERβ expression plasmid used in their study had a mutation of 310 glutamic acid (E) to glycine (G).